## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | What treatments work for anxiety in children with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)?: A Systematic Review |
| **AUTHORS** | Stoll, Sarah; Crawley, Esther; Richards, Victoria; Lal, Nishita; Brigden, Amberly; Loades, Maria |

## VERSION 1 - REVIEW

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| **REVIEWER** | Anilena Mejia<br>Instituto de Investigaciones Científicas y Servicios de Alta Tecnología, INDICASAT AIP<br>Panamá |
| **REVIEW RETURNED** | 31-Jan-2017 |

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| **GENERAL COMMENTS** | This is a systematic review intending to explore best treatment approaches for anxiety in children with CFS/ME. This is an important research question yet to be answered given the high rates of anxiety in patients with CFS/ME. The manuscript is well-written and structured appropriately. However, I have several concerns.<br><br>1. The fact that authors found 5 articles by hand searching, which did not come up in their formal search, makes me wonder whether their search strategy was comprehensive enough. For example, I see they missed important databases such as CINAHL.<br><br>2. Their inclusion/exclusion criteria is not clearly stated. My understanding is that they only included studies in which anxiety was measured as an outcome, regardless of whether the intervention was targeting anxiety in particular. If so, 8 studies seem like very little, as most intervention studies of CFS/ME include anxiety as a secondary outcome measure. How were they excluding studies? I will suggest they review their methods and make sure they are providing enough detail to make the study replicable.<br><br>3. In the last paragraph of the Introduction they are providing about 5 aims. To me, their overall aim is not clear. Did they wanted to know whether treatment for CFS/ME in children also had an effect on anxiety levels? Given that none of the interventions were targeting anxiety in particular, this is the only question they could answer.<br><br>Overall, I think the study proposes an important research question but the manuscript requieres more consistency throughout. Aims need to be clearly stated and methods need to be more specific, in order to assess whether authors were able to answer the research question appropriately. |

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| **REVIEWER** | Hiran Thabrew<br>University of Auckland, New Zealand |
| **REVIEW RETURNED** | 20-Feb-2017 |

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| **GENERAL COMMENTS** | This systematic review addresses an area of increasing clinical concern - that of children with chronic illness who have co-morbid psychological problems. As stated, children with chronic fatigue syndrome are at almost 40% risk of developing an anxiety disorder, particularly separation anxiety and social phobia. Treatment of mental health problems in children and adolescents with chronic fatigue syndrome is often based on evidence-based paradigms designed for the general population, despite the likely relationship between illness and treatment-related experiences and the onset and recovery from psychological issues in this group.<br><br>The authors present a clearly defined systematic review of treatment for anxiety in paediatric chronic fatigue syndrome. The aims, key outcomes, methods, results and conclusions are all succinctly and reasonably presented.<br><br>As mentioned in the text, strengths of the study include the multi-database search strategy and inclusion of articles in languages other than English. Despite this, the number of studies identified was small and none was designed to measure change in anxiety as a primary outcome. In addition, the types of measures used to assess anxiety were too heterogenous to allow any meta-analysis, leaving statistically-based conclusions impossible to make. The authors have accurately identified regression to the mean and spontaneous improvement in anxiety over time (common in relapsing/remitting psychological conditions) as possible explanations for improvement in studies that attributed change to the use of mainly CBT-based interventions. Unsatisfying as they are, the conclusions drawn reflect the limited nature of the current evidence base in this area and are accurately presented. Appropriate reference is made to overlapping reviews by Knight and Bennett.<br><br>The PRISMA checklist did not have any page numbers included, however apart from this, there were no obvious concerns to mention with regard to its acceptability. If this article is considered to be of suitable interest for the audience of this journal, I would support its publication. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. The fact that authors found 5 articles by hand searching, which did not come up in their formal search, makes me wonder whether their search strategy was comprehensive enough. For example, I see they missed important databases such as CINAHL.

Thank you. We agree the search strategy has missed those important articles. We therefore re-ran the search excluding anxiety in our search terms as we found that many studies measuring anxiety as a secondary outcome were being excluded. This appeared to solve the problem with all articles now being found in the search. In doing so we found an additional article by Rimes et al 2014 that was linked to the study by Lloyd et al 2012 by using a sub-sample of the participants in the Lloyd et al study.

2. Their inclusion/exclusion criteria is not clearly stated. My understanding is that they only included studies in which anxiety was measured as an outcome, regardless of whether the intervention was targeting anxiety in particular. If so, 8 studies seem like very little, as most intervention studies of CFS/ME include anxiety as a secondary outcome measure. How were they excluding studies? I will suggest they review their methods and make sure they are providing enough detail to make the study replicable.

Thank you. We have also now reviewed the methods and re-ran the search excluding anxiety in our search terms. In doing this we had significantly more articles to screen (1074 after removal of duplicates). We also found an additional study to include in the systematic review, totalling this up to 9 studies.
We have clarified the inclusion and exclusion criteria by putting this in the first paragraph and replacing the previous paragraph. This now reads:

We included observation studies or treatment trials which recruited participants with the following characteristics:
• Children <18 years of age
• Diagnosed wiith CFS/ME (chronic fatigue syndrome/myalgic encephalitis or myalgic encephalopathy) defined using CDC criteria (Fukuda 1994, 2004) or NICE (2007) or Oxford criteria
• Participants have completed a valid assessment of anxiety at baseline

3. In the last paragraph of the Introduction they are providing about 5 aims. To me, their overall aim is not clear. Did they wanted to know whether treatment for CFS/ME in children also had an effect on anxiety levels? Given that none of the interventions were targeting anxiety in particular, this is the only question they could answer.

Thank you. We agree. The previous aims were research questions (as listed on PROSPERO), we have deleted these and we have kept the original aims. Please see response to the editor above.

Overall, I think the study proposes an important research question but the manuscript requieres more consistency throughout. Aims need to be clearly stated and methods need to be more specific, in order to assess whether authors were able to answer the research question appropriately.

Thank you. We agree. We have taken this opportunity to improve the flow and the writing of the paper. There are many changes which can be seen in the tracked change version. Some of the important changes are included below:

In the results section on page 8: “Of the six treatment studies, four used a CBT approach, one used a behavioral approach and one used intravenous gammaglobulin. The primary outcomes included fatigue(22-24, 26, 27, 30), disability or function(28)and school attendance in(22, 24-27, 30). All studies measured anxiety as a secondary outcome.

The common elements of all five cognitive behavioural and behavioural interventions appear to be the inclusion of a graded approach to managing activity, and employing strategies to address cognitive elements such as illness related beliefs and negative predictions about the future where necessary (see table 2 for details). Interventions varied considerably in the duration of treatment (12 weeks to 1 year), length of sessions (no direct therapist contact/30 minutes/60 minutes), and treatment modality (face-to-face, telephone, internet delivered modules with therapist e-consults).”

“Studies using a CBT approach:

The duration of CBT across the studies ranged from six 30 minute telephone sessions at fortnightly intervals(24, 25), to twenty-one internet session modules over 26 weeks(26, 27, 31). In three of the four studies, the authors report that, anxiety improved with treatment, which suggests that cognitive behavioural treatment for CFS/ME may improve anxiety (table 3).

Nijhof et al's (2012, 2013) RCT compared internet-based CBT to traditional methods in 135 participants. The internet-based CBT, FITNET, includes psycho-educational modules for patients and parents in addition to CBT modules developed by the Expert Centre for Chronic Fatigue(26, 27). Patients were able to send emails and therapists replied to 'e-consults' on the same day each week or depending the treatment plan. At 6 months, the study found a significant improvement in school attendance (full time school 75% in FITNET group compared to 16% in usual care group), fatigue and physical function in those receiving FITNET with 63% defined as "recovered" defined using primary and secondary outcome compared to 8% of those receiving treatment as usual."

In the discussion section, page 14 paragraph 3: "Only eight studies were found with most having small sample sizes. None were powered to determine treatment efficacy in those with CFS/ME and anxiety. Only three of the studies were RCTs and one excluded those with high anxiety scores(26-28, 30)making it difficult to investigate treatment effects in those with co-morbid anxiety. None of the studies included children who were 10 years old and younger and therefore we do not know about treatment efficacy in this group(26)"

Reviewer: 2

The PRISMA checklist did not have any page numbers included, however apart from this, there were no obvious concerns to mention with regard to its acceptability. If this article is considered to be of suitable interest for the audience of this journal, I would support its publication.
Thank you. We have added page numbers to the PRISMA check list.

In addition, we feel it would be more appropriate if I am the corresponding author and we have made the necessary changes. As we re-ran the search we also recruited three more authors for their assistance who have been added to the paper.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Hiran Thabrew<br>University of Auckland, New Zealand |
| **REVIEW RETURNED** | 26-May-2017 |

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| **GENERAL COMMENTS** | All concerns identified during the initial review process have been explicitly addressed. |